# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Lacidipine 4 mg Film-coated Tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4 mg lacidipine.

Excipient (s) with known effect:
Each 4 mg tablet contains 400 mg of lactose

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

White, biconvex, oval film-coated tablets, debossed "4", breakline and "LC" on one side, plain on the other. The tablet can be divided into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lacidipine is indicated for the treatment of hypertension either alone or in combination with other antihypertensive agents, including β-adrenoceptor antagonists, diuretics, and ACE-inhibitors.

### 4.2 Posology and method of administration

Method of administration
For oral administration

Posology

Adults:
The treatment of hypertension should be adapted to the severity of the condition, and according to the individual response.

The recommended initial dose is 2 mg once daily, preferably in the morning, with or without food. The dose may be increased to 4 mg (and then, if necessary, to 6 mg) after adequate time has been allowed for the full pharmacological effect to occur. In practice, this should not be less than 3 to 4 weeks, unless the clinical condition requires a more rapid upward titration Daily doses above 6 mg have not been shown to be significantly more effective.

Lacidipine should be taken at the same time each day, preferably in the morning.

Patients with hepatic impairment:
No dose modification is required in patients with hepatic impairment.

Patients with renal impairment:
As Lacidipine is not cleared by the kidneys, the dose does not require modification in patients with renal impairment.

Paediatric population:
Because no experience has been gained with lacidipine relating safety and efficacy in children, this is not recommended for children and adolescents under 18 years old.

Older people:
No dose modification is required. Treatment may be continued indefinitely.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Lacidipine should only be used with great care in patients with a previous allergic reaction to another dihydropyridine because there is a theoretical risk of cross-reactivity.

- As with other dihydropyridines, lacidipine is contraindicated in patients with severe aortic stenosis.

## 4.4 Special warnings and precautions for use

In specialised studies lacidipine has been shown not to affect the spontaneous function of the sinoatrial (SA) node or to cause prolonged conduction within the atrioventricular (AV) node. However, the theoretical potential for a calcium channel antagonist to affect the activity of the SA and AV nodes should be noted, and therefore Lacidipine should be used with caution in patients with pre-existing abnormalities in the activity of the SA and AV nodes.

As has been reported with certain dihydropyridine calcium channel antagonists, lacidipine should be used with caution in patients with congenital or documented acquired QT prolongation. Lacidipine should also be used with caution in patients treated concomitantly with medications known to prolong the QT interval such as class I and III antiarrhythmics, tricyclic antidepressants, some antipsychotics, antibiotics (e.g. erythromycin) and some antihistamines (e.g. terfenadine).

As with other calcium antagonists, lacidipine should be used with caution in patients with poor cardiac reserve.

As with other dihydropyridine calcium antagonists, lacidipine should be used with care in patients with unstable angina pectoris as well as in patients who develop unstable angina during treatment.

Lacidipine should be used with caution in patients after recent myocardial infarction.
There is no evidence that lacidipine is useful for secondary prevention of myocardial infarction.
The efficacy and safety of Lacidipine in the treatment of malignant hypertension has not been established.

Lacidipine should be used with caution in patients with impaired liver function because antihypertensive effect may be increased.
There is no evidence that lacidipine impairs glucose tolerance or alters diabetic control.

Excipients
*Lactose*
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
*Sodium*
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of Lacidipine with other agents recognised to have a hypotensive effect including antihypertensive agents (e.g. diuretics, beta-blockers or ACE-inhibitors) may have an additive hypotensive effect. However, no specific interaction problems have been identified in studies with common antihypertensive agents (e.g. beta-blockers and diuretics) or with digoxin, tolbutamide or warfarin.

The plasma level of lacidipine may be increased by simultaneous administration of cimetidine.

Lacidipine is highly protein-bound (>95%) to albumin and alpha-1-glycoprotein.

As for all vasodilatory antihypertensives, caution is mandatory if alcohol is consumed concomitantly, as this can enhance their effects.

As with other dihydropyridines, Lacidipine should not be taken with grapefruit juice as bioavailability may be altered.

No specific pharmacodynamic interaction problems have been identified in studies with common antihypertensive agents or with tolbutamide or warfarin.

In a clinical study in patients with a renal transplant treated with ciclosporine, lacidipine reversed the decrease in renal plasma flow and glomerular filtration rate induced by ciclosporin.

Lacidipine is known to be metabolised by cytochrome CYP3A4 (e.g. rifampicine, itraconazole) and, therefore significant inhibitors and inducers of CYP3A4 (e.g. rifampicine, itraconazole) administered concurrently may interact with the metabolism and elimination of lacidipine.

Concomitant use of lacidipine and corticoids or tetracosactide might decrease antihypertensive effect.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
There are no data on the safety of lacidipine in human pregnancy.
Animal studies have shown no teratogenic effects or growth impairment (see section 5.3 Preclinical safety data). Lacidipine should only be used in pregnancy when the potential benefits for the mother outweigh the possibility of adverse effects in the foetus or neonate.

The possibility that lacidipine can cause relaxation of the uterine muscle at term should also be considered (see section 5.3 Preclinical safety data).

**Breastfeeding**
Milk transfer studies in animals have shown that lacidipine (or its metabolites) are likely to be excreted into breast milk.

Lacidipine should only be used during lactation when the potential benefits for the mother outweigh the possibility of adverse effects in the foetus or neonate.

**Fertility:**
Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by channel blockers.

### 4.7 Effects on ability to drive and use machines

Lacidipine may cause dizziness. Patients should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

### 4.8 Undesirable effects

Data from large clinical trials (internal and published) were used to determine the frequency of very common to uncommon adverse effects.

The following convention has been used for the classification of frequency: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥1/1,000 to <1/100, rare ≥1/10,000 to <1/1,000, very rare <1/10,000, not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Lacidipine is usually well tolerated. Some patients may experience minor adverse effects which are related to its known pharmacological action of peripheral vasodilation. Such effects, indicated by a hash (#), are usually transient and usually disappear with continued administration of lacidipine at the same dosage.

| **System Organ Class** | **Adverse reaction** |
|---|---|
| **Psychiatric disorder** | |
| **Very rare** | Depression |
| **Nervous system disorders** | |
| Common | #Headache, #dizziness |
| Rare | Depression |
| Very rare | Tremor |
| Unknown | Extrapyramidal syndrome has been reported with some calcium inhibitors |
| **Cardiac disorders** | |
| Common | #Palpitation, tachycardia |
| Uncommon | Aggravation of underlying angina syncope, hypotension |
| As with other dihydropyridines aggravation of underlying angina has been reported in a small number of individuals, especially at the start of treatment. This is more likely in patients with symptomatic ischaemic heart disease. | |
| **Vascular disorders** | |
| Common | #Flushing |
| **Gastrointestinal disorders** | |
| Common | Stomach discomfort, nausea |
| Uncommon | Gingival hyperplasia |
| **Skin and subcutaneous tissue disorders** | |
| Common | Skin rash (including erythema and itching) |
| Rare | Angioedema, urticaria |
| Musculoskeletal and connective tissue disorders | |
| Rare | Muscle cramps |
| **Renal and urinary disorders** | |
| Common | Polyuria |
| **General disorders and administration site conditions** | |
| Common | Asthenia, #oedema |
| **Investigations** | |
| Common | Reversible increase in alkaline phosphatase (clinically significant increases are uncommon). |

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

There have been no recorded cases of lacidipine overdosage.

Symptoms and Signs
The most likely problem would be prolonged peripheral vasodilation associated with hypotension and tachycardia. Bradycardia or prolonged AV conduction could theoretically occur.

Treatment:
There is no specific antidote. Standard general measures for monitoring cardiac function and appropriate supportive and therapeutic measures should be used.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dihydropyridine derivates. ATC code: C08CA09

Lacidipine is a specific and potent calcium channel antagonist with a predominant selectivity for calcium channels in the vascular smooth muscle.
Its main action is to dilate peripheral arterioles, reducing peripheral vascular resistance and lowering blood pressure.
Following the oral administration of 4 mg lacidipine to healthy volunteers, a minimal prolongation of QT interval has been observed (mean QTcF increase between 3.44 and 9.60 ms in young and elderly volunteers).

### 5.2 Pharmacokinetic properties

Lacidipine is a highly lipophilic compound; it is rapidly but poorly absorbed from the gastrointestinal tract following oral dosing. It undergoes extensive first-pass metabolism in the liver. Absolute bioavailability averages about 10 %. Peak plasma concentrations are reached between 30 and 150 minutes after administration.

During metabolism of lacidipine, 4 principal metabolites are formed, which possess little, if any pharmacodynamic activity.

The drug is eliminated primarily by hepatic metabolism (involving P450 CYP3A4). There is no evidence that lacidipine causes either induction or inhibition of hepatic enzymes.
Approximately 70 % of the administered dose is eliminated as metabolites in the faeces and the remainder as metabolites in the urine.
The average terminal plasma half-life of lacidipine ranges from between 13 and 19 hours at steady state.

### 5.3 Preclinical safety data

The only significant toxicological findings with lacidipine were reversible and consistent with the known pharmacological effects of calcium channel antagonists at high doses - decreased myocardial contractility and gingival hyperplasia in rats and dogs, and constipation in rats.

No evidence of developmental toxicity was seen following administration of lacidipine to pregnant rats or rabbits.

Lacidipine was not genotoxic in a battery of *in vitro* and *in vivo* tests. There was no evidence of carcinogenic potential in mice. Consistent with other calcium channel antagonists, there was an increase in benign interstitial cell tumours in testis in a carcinogenicity study in rats. However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Povidone K-30
Lactose
Sodium starch glycolate Type A
Magnesium stearate

Film coating:

AquaPolish white 015.10 SP containing
Titanium dioxide (E171)
Hydroxypropylmethylcellulose (E464)
Gum arabicum (E414)
Lactose monohydrate
Talcum (E553b)

### 6.2 Incompatibilities

Not *applicable*

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

OPA/Al/PVC-Al blister.
Available in packs of 14, 15, 28, 30, 56, 60, 84, 90, 98 and 100 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

## 8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1399

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2015

## 10. DATE OF REVISION OF THE TEXT

03/07/2020

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## Teva Pharmaceuticals Europe B.V

## 1.3.1 spc-uk-pl-00289-1399-lacidipine-4mg-film-coated-tablets

# APPROVALS

| Signed by | Meaning of Signature | Server Date |
|---|---|---|
| Justyna Malinowska | Regulatory Affairs Approval | 07-Jul-2020 04:36:03 PM |